Azapeptide Carbonyls: A New Class of 20S Proteasome Inhibitors

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What did I learn?

From my summer experiences at CBEC laboratories, I learned how to apply my organic chemistry knowledge into concrete, real-world application. This included the general awareness of organic chemistry reactions along with more specific laboratory practical knowledge.

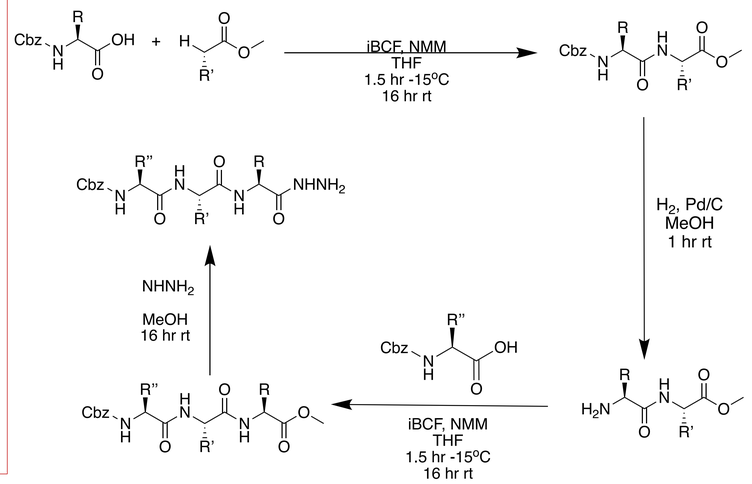
For this research, this was heavily focused on peptide (protein) synthesis procedures, along with purification and analytical analysis (which was done by NMR and ESI). This experience helped me figure out how to approach laboratory issues more direct and professionally. Such as knowing how recover any spilled product, or how to purify specific peptides. By knowing how to approach these issues directly and with experience, it can benefit future professions in working in a synthetic laboratory setting.

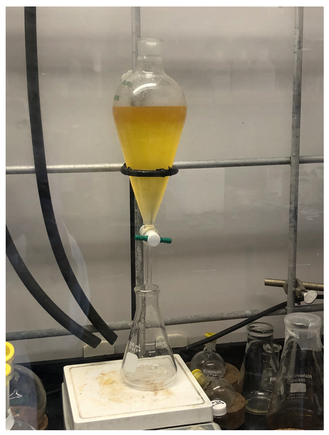
Introduction

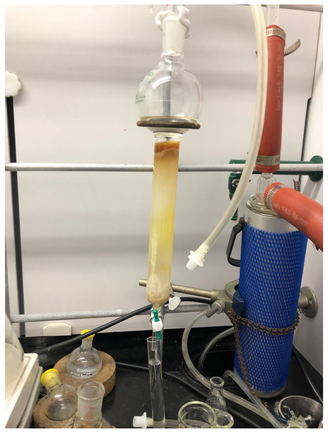
The 26S proteasome is a critical component of the ubiquitin-proteasome pathway (UPP) that is responsible for the quality control of newly synthesized proteins in eukaryotic cells. The substrates in the UPP are involved in the cell cycle as well as apoptosis. This makes the proteasome an important target for cancer treatment, in particular, for multiple myeloma (MM).

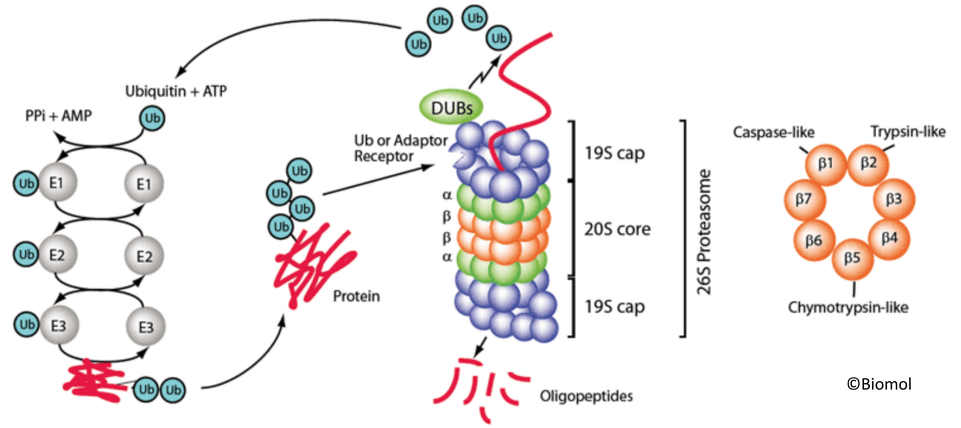
The 20S core of the proteasome contains 7 different subunits of α-types in the outer rings of the barrel and β-types both in the inner parts. Their N-terminal threonine residue released from the precursor processing causes a nucleophilic attack for peptide bond hydrolysis. In particular, β-type active sites: Caspase-like, Trypsin-like, and the Chymotrypsin-like active sites have been identified for different peptidolytic activities. The Chymotrypsin-like active site cleaves to the C-terminal phenylalanine, tryptophan, and tyrosine peptide chains.

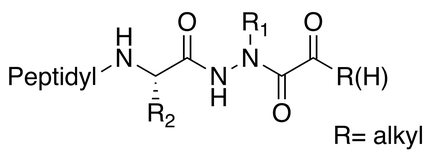
The goal for this research to is create a new design of inhibitor that allows for the inhibitor to target the 20S core with more specificity and selectivity which can allow for more direct inhibition. This is done by changing the α-carbon with a nitrogen.



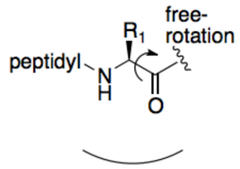




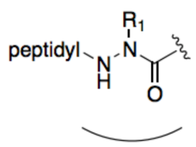




aza-peptide carbonyl design



P1 residue



aza-P1 residue

What motivated me to do this project?

The motivation behind this project is to explore new means of medical treatments. Recently, targeting inhibition therapy have become popular for treatments and is a popular topic in the research community. The research behind these therapies even tackle the most complicated cases of diseases, such as Alzheimer's disease and HIV. This research project allows me to dive into how these treatments are made and how the process of deciding how to create a more selective approach in inhibiting a disease can be time consuming, but worth-while for the best results.

What was transformational about the project?

The project was helpful by narrowing down my future career paths. Currently, as a pre-medicine student doing research, I was not sure if I wanted to go to medical school. The lab experienced made me realize that I did want to pursue a research career whether it be in the medical field or at a private chemical company. I know that I would like to work in a type of laboratory setting with the opportunity to form and work up my own data.

What was my favorite part of the experience?

My favorite part was when I got to present my data at the group meetings. This allowed me to interact with professors, PhD students, and other graduate and undergraduate students of different chemistry practices. I enjoyed the challenge of answering complex questions, and having other point out certain data points, mechanisms, reactions, etc. that I can change to improve my synthesis process, working up a reaction, or analytical techniques. The input from not only the professors and PhD students, but also the undergraduates and graduate students were extremely helpful in improving my lab practical techniques and the utilization of applying my organic chemistry knowledge into my research.

Another favorite was the synthesis process of creating peptide bonds. At first, the process was a little complicated that required over 2-3 days of work just to produce a dipeptide (a protein with two amino acids). But the result was worth the time, for these dipeptides, tripeptides, and tetrapeptides being created would be used in an in vitro kinetic research. The whole experience made me feel great knowing that I was making a contribution in the field.

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